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| 10/789,180 | 02/26/2004 | Catherine C. Turkel | 17679 (BOT) | 9912 |

7590 05/10/2011

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| EXAMINER | |
|---|---|
| FORD, VANESSA L | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1645 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/789,180 | TURKEL ET AL. | |
| | Examiner | Art Unit | |
| | VANESSA L. FORD | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 February 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-3,5-16,18-20 and 29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-16,18-20 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 June 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## FINAL ACTION

1. Applicant's amendment and response filed February 28, 2011. Claims 1-2, 9, 16 and 18 have been amended. Claims 4, 17 and 21-28 have been canceled.

Claims 1-3, 5-16, 18-20 and 29 are under examination.

### *Rejections Withdrawn*

2. In view of Applicant's amendment and remarks the following rejections are withdrawn:

(a) rejection of claims 1-20 and 29 under 35 U.S.C. 112 first paragraph, pages 3-5, paragraph 3.

(b) rejection of claims 5 and 8 under 35 U.S.C. 112 second paragraph, page 4, paragraph 4.

### *Rejections Maintained*

3. The rejection under 35 U.S.C. 103(a) is maintained for claims 1-3, 10-16, 19-20 and 29 for the reasons set forth on pages 6-10, paragraph 5 of the previous Office Action.

The following rejection is maintained and reiterated below:

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The claims are rejected under 35 U.S.C. 103(a) as unpatentable over Schim *(Current Medical Research and Opinion, Vol. 20, No,1, January 2001, p. 49-53)* in view

of Johnson et al *(U.S. Patent No. 5,512, 547 issued April 30, 1996)* in view of *Cephalalgia, An International Journal of Headache*, Volume 24, Supplement 1, 2004 (*Cephalalgia, 2004*) and further in view of Aoki et al *(U.S. Patent No. 6,896,886 B2 filed July 16, 2001, issued May 24, 2005).*

Independent claim 1 is directed to a method of treating an acute pain medication overuse disorder caused by overuse of acute pain medication, the method comprising the step of local administration of between about 1 unit and about 1500 units of a pure botulinum toxin type A or B, wherein the pure botulinum toxin has a molecular weight of about 150 kDa, to a patient with acute pain medication thereby treating the acute pain medication overuse disorder caused by overuse of acute pain medication, wherein the patient takes the medication prior to experiencing pain and experiences pain after the intake of acute pain medication thereby treating the acute pain medication overuse disorder caused by the overuse of acute pain medication.

Schim teaches a method of treating medication overuse disorder by administering to a patient botulinum toxin (includes complexing proteins) (page 51). Schim teaches this method because Schim teaches that botulinum toxin was administered to patients with and without analgesic overuse (Study 3, page 51). Schim teaches that botulinum toxin was effective in treating patients with medication overuse disorder (page 51).

Schim do not teach pure botulinum toxin.

Johnson et al teach that pure botulinum toxin (without complexing proteins) has advantages over the botulinum toxin complex because of their high percentage recovery of biologically active neurotoxin and their long-term stability (shelf-life) at temperatures of 0°C which in contrast to the current commercial available products that have a low percentage recovery of biological active neurotoxin and must be stored at temperatures of -10°C or less (column 4).

Schim and Johnson et al do not specifically teach the claim limitations “wherein the patient takes the medication prior to experiencing pain and experiences pain after the intake of acute pain medication thereby treating the acute pain medication overuse disorder caused by the overuse of acute pain medication”.

*Cephalalgia* teaches that medication-overuse is an interaction between a therapeutic agent and used excessively and susceptible patient (page 94). *Cephalalgia* teaches that the best example is overuse of symptomatic headache drugs causing headache in the headache-prone patient (page 94). (*Cephalalgia, 2004*), which teaches that the most common migraine-like headache occurs on ≥ 15 days per month and occur as a mixture of migraine-like and tension-like headaches (page 94). *Cephalalgia, 2004* teach that these patients overuse migraine drugs and /or analgesics (page 94). *Cephalalgia, 2004* teach that diagnostic criterion used for these patients is ≥ 10 days per month of drug use, this translates into 2-3 treatment days a week (page 94). Based on the definition given by *Cephalalgia*, the claim limitations “wherein the patient takes the medication prior to experiencing pain and experiences pain after the intake of acute pain medication thereby treating the acute pain medication overuse disorder caused by the overuse of acute pain medication” are necessarily taught in the art because Schim teaches the treatment of "medication overuse patients".

Schim, Johnson et al and Cephalalgia do not specifically teach intradermal administration.

Aoki et al teach that botulinum toxin can be used to treat various disorders including headaches and conditions associated with pain (see the Abstract and column 10, Example 11). Aoki et al teach that botulinum toxin can be used to treat patients by intradermal administration (column 10, claim 3).

It would be prima facie obvious at the time the invention was made to substitute the botulinum toxin complex as taught by Schim for the pure botulinum toxin as taught by Johnson et al by intradermal administration as taught by Aoki et al used in a method of treating medication overuse disorder (defined by Cephalalgia) because Johnson et al teach that high specific activity preparations reduce the probability of patients developing neutralizing antibodies and it obviously would be desirable to have higher specific activity preparations than those currently available and Aoki et al teach that botulinum toxin can be used to treat patients by intradermal administration. Additionally, Johnson et al teach that the primary advantageous of the compositions of the invention are their high percentage recovery of biologically active neurotoxin and their long-term stability (shelf-life) at temperatures of 0°C which in contrast to the current commercial available products that have a low percentage recovery of biological active neurotoxin and must be stored at temperatures of -10°C or less.

It would be expected, absent evidence to the contrary, that administering intradermally a composition comprising pure botulinum toxin would be effective in treating medication disorder as well as requiring a lower dosage of botulinum toxin and minimize the development of neutralizing antibodies in these patients.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method, and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". Thus, the combination of prior art references as combined provided a *prima facie* case of obviousness.

Applicant's Arguments

Applicant urges that the claimed invention is not obvious. Applicant urges that to establish a prima facie case of obviousness the Office must meet four conditions. Applicant urges that the Office must show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process, the Office must show that the prior art itself would have provided one of ordinary skill in the art with a reasonable expectation of success, the prior art must teach or suggest all the claim limitations and if an obviousness rejection is based on some combination of prior art references, the Office must show a suggestion, teaching or motivation to combine the prior art references.

Applicant urges that Tepper is a poster presentation that discusses botulinum toxin administration in the preventative treatment of refractory headaches (treatment of refractory headaches in patients that are medication overusers as well as non-overusers. Applicant urges that Tepper does not suggest method of treating patients suffering from an acute pain medication overuse disorder. Applicant urges that Tepper provides no administration beyond the fact the each patient had received 100 units of botulinum toxin A.

Applicant urges that Johnson et al teach the use of a pure toxin. Applicant urges that the reference does not at any point state that the pure toxin is pharmacologically equivalent to the toxin complex used in Tepper. Applicant urges that shelf-life and immunogenicity are no benefit if the new molecule does not perform as

well as the old molecule. Applicant urges that Johnson et al gives no indication that pure toxin works as well as the complex.

Applicant urges that neither Cephalalgia 2004 nor Aoki cannot remedy the shortcomings of Tepper. Applicant urges that a skilled artisan in view of Tepper would likely believe that medication overuse leads to reductions in headache frequency because Tepper shows there is a lower occurrence of headache in medication "overusers" than "non-overusers" at baseline. It should be noted that Applicant does not address the Schim reference.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed February 28, 2011 have been fully considered but they are not persuasive.

In response to applicant's argument that there is no teaching, suggestion, or motivation to combine the references, the examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007). In this case,.

- Schim teaches a method of treating medication overuse disorder by administering to a patient botulinum toxin (includes complexing proteins).

- Johnson et al teach that pure botulinum toxin (without complexing proteins) has advantages over the botulinum toxin complex because of their high percentage recovery of biologically active neurotoxin and their long-term stability (shelf-life) at temperatures of 0°C which in contrast to the current commercial available products that have a low percentage recovery of biological active neurotoxin and must be stored at temperatures of -10°C or less.
- *Cephalalgia* teaches that medication-overuse is an interaction between a therapeutic agent and used excessively and susceptible patient (page 94). *Cephalalgia* teaches that the best example is overuse of symptomatic headache drugs causing headache in the headache-prone patient (page 94). (*Cephalalgia, 2004*), which teaches that the most common migraine-like headache occurs on ≥ 15 days per month and occur as a mixture of migraine-like and tension-like headaches (page 94). *Cephalalgia, 2004* teach that these patients overuse migraine drugs and /or analgesics (page 94). *Cephalalgia, 2004* teach that diagnostic criterion used for these patients is ≥ 10 days per month of drug use, this translates into 2-3 treatment days a week (page 94). Based on the definition given by *Cephalalgia*, the claim limitations "wherein the patient takes the medication prior to experiencing pain and experiences pain after the intake of acute pain medication thereby treating the acute pain medication overuse disorder caused by the overuse of acute pain

medication" are necessarily taught in the art because Schim teaches the treatment of "medication overuse patients".

- Aoki et al teach that botulinum toxin can be used to treat various disorders including headaches and conditions associated with pain (see the Abstract and column 10, Example 11). Aoki et al teach that botulinum toxin can be used to treat patients by intradermal administration (column 10, claim 3).

One of ordinary skill in the art would be motivated to substitute the botulinum toxin complex as taught by Schim for the pure botulinum toxin as taught by Johnson et al by intradermal administration as taught by Aoki et al used in a method of treating medication overuse disorder (defined by Cephalalgia) because Johnson et al teach that high specific activity preparations reduce the probability of patients developing neutralizing antibodies and it obviously would be desirable to have higher specific activity preparations than those currently available and Aoki et al teach that botulinum toxin can be used to treat patients by intradermal administration.

To address Applicant's arguments regarding the pure toxin not working as well as the complex, it should be noted that the purified toxin is botulinum toxin without complexing proteins. Johnson et al teach that pure toxin allows the artisan of ordinary skill to reduce the amount of toxin used in required the units per vial (column 2). Therefore, by reading Johnson et al the artisan of ordinary skill would use the pure toxin instead of the complex because less of the pure toxin is needed per dosage and the shelf-life of the pure toxin is sufficiently longer.

In view of all of the above, the combination of prior art references teach the claimed invention, absent convincing evidence to the contrary.

4. The rejection under 35 U.S.C. 103(a) is maintained for claims 1-3, 5-16,18-20 and 29 for the reasons set forth on pages 11-14, paragraph 6 of the previous Office Action.

The following rejection is maintained and reiterated below:

The claims are rejected under 35 U.S.C. 103(a) as unpatentable over Tepper et al *(Cephalagia, 2003, 23, 581-762)* in view of Johnson et al *(U.S. Patent No. 5,512, 547 issued April 30, 1996)* in view of *Cephalalgia, An International Journal of Headache*, Volume 24, Supplement 1, 2004 (*Cephalalgia, 2004*) and further in view of Aoki et al *(U.S. Patent No. 6,896,886 B2 filed July 16, 2001, issued May 24, 2005).*

Independent claim 1 is directed to a method of treating an acute pain medication overuse disorder caused by overuse of acute pain medication, the method comprising the step of local administration of a pure botulinum toxin, wherein the pure botulinum toxin has a molecular weight of about 150 kDa, to a patient with acute pain medication thereby treating the acute pain medication overuse disorder caused by overuse of acute pain medication, wherein the patient takes the medication prior to experiencing pain and experiences pain after the intake of acute pain medication thereby treating the acute pain medication overuse disorder caused by the overuse of acute pain medication.

Tepper et al teach a method of treating medication overuse disorder by administering to a patient botulinum toxin (includes complexing proteins) (page 715). Tepper et al teach that the patients were administered 100 units of botulinum toxin A (page 715). Tepper et al teach that botulinum toxin was effective in treating patients with medication overuse disorder (page 715).

Tepper et al do not teach pure botulinum toxin.

Johnson et al teach that pure botulinum toxin (without complexing proteins) has advantages over the botulinum toxin complex because of their high percentage recovery of biologically active neurotoxin and their long-term stability (shelf-life) at temperatures of 0°C which in contrast to the current commercial available products that have a low percentage recovery of biological active neurotoxin and must be stored at temperatures of -10°C or less (column 4).

Tepper et al and Johnson et al do not specifically teach the claim limitations "wherein the patient takes the medication prior to experiencing pain and experiences pain after the intake of acute pain medication thereby treating the acute pain medication overuse disorder caused by the overuse of acute pain medication".

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- Johnson et al teach that pure botulinum toxin (without complexing proteins) has advantages over the botulinum toxin complex because of

their high percentage recovery of biologically active neurotoxin and their long-term stability (shelf-life) at temperatures of 0°C which in contrast to the current commercial available products that have a low percentage recovery of biological active neurotoxin and must be stored at temperatures of -10°C or less.

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In view of all of the above, the combination of prior art references teach the claimed invention, absent convincing evidence to the contrary.

***Status of Claims***

5. No claims allowed.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

## *Conclusion*

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to VANESSA L. FORD whose telephone number is (571)272-0857. The examiner can normally be reached on 9 am- 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571.272.0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Vanessa L. Ford/
Primary Examiner, Art Unit 1645
May 7, 2011